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WO 01/56573 A1

(54) Title: USE OF COX-2 INHIBITORS AS GASTROPROKINETICS

(57) Abstract: The invention provides a COX-2 inhibitor or a pharmaceutically acceptable derivative thereof for use in the treatment of a disorder ameliorated by a gastroprokinetic.

USE OF COX-2 INHIBITORS AS GASTROPROKINETICS

The invention relates to a new medical use for compounds which act as inhibitors of cyclooxygenase-2 (COX-2).

It is only recently that the enzyme COX has been discovered to exist in two isoforms, COX-1 and COX-2. COX-1 corresponds to the originally identified constitutive enzyme while COX-2 is rapidly and readily inducible by a number of agents including mitogens, endotoxin, hormones, cytokines and growth factors. Prostaglandins generated by the action of COX have both physiological and pathological roles. It is generally believed that COX-1 is largely responsible for the important physiological functions such as maintenance of gastrointestinal integrity and renal blood flow. In contrast the inducible form, COX-2, is believed to be largely responsible for the pathological effects of prostaglandins where rapid induction of the enzyme occurs in response to such agents as inflammatory agents, hormones, growth factors and cytokines. A selective inhibitor of COX-2 would therefore have anti-inflammatory, anti-pyretic and analgesic properties, without the potential side effects associated with inhibition of COX-1.

COX-2 inhibitors may be identified by methods well known in the art, for example as described in WO99/12930 (especially pages 25 and 26).

In various animal models, by-products of the COX pathway have been shown to be inhibitory to gastrointestinal motility. Specifically, stimulation in motor activity occurs following administration of non-selective COX inhibitors, such as indomethacin, and inhibition in motor activity follows exogenous administration of some prostaglandins. Additionally, intravenous administration of indomethacin has also been shown to increase lower esophageal sphincter pressure (LESP) in man. The observed changes in motor activity have been attributed to products of the COX-1 pathway, since the trigger for induction of COX-2, the inducible isoform of the COX enzyme, is not readily apparent.

Surprisingly, it has now been found that COX-2 inhibitors stimulate gastrointestinal motility and hence act as gastroprokinetics.

Accordingly, COX-2 inhibitors are of use in the treatment of disorders ameliorated by a gastroprokinetic. Disorders ameliorated by gastroprokinetic agents include ileus, for example post-operative ileus and ileus during sepsis; gastroesophageal reflux disease (GORD, or its synonym GERD); gastroparesis, such as diabetic gastroparesis; and other functional bowel disorders, such as non-ulcerative dyspepsia (NUD) and non-cardiac chest pain (NCCP).

According to one aspect, the invention therefore provides a method of treatment of a mammal, including man, suffering from a disorder ameliorated by a gastroprokinetic which comprises administering an effective amount of a COX-2 inhibitor or a pharmaceutically acceptable derivative thereof.

In another aspect, the invention provides the use of a COX-2 inhibitor or a pharmaceutically acceptable derivative thereof in the manufacture of a medicament for the treatment of a disorder ameliorated by a gastroprokinetic.

By pharmaceutically acceptable derivative is meant any pharmaceutically acceptable salt or solvate of a COX-2 inhibitor or any other compound, which upon administration to the recipient is capable of providing (directly or indirectly) a COX-2 inhibitor or an active metabolite or residue thereof.

A number of COX-2 inhibitors have been disclosed, for example those mentioned in the following patent applications:

AU9719132,	CA2164559,	CA2180624,	EP-799823,	EP-846689,
EP-863134,	FR2751966,	GB2283745,	GB2319772,	GB2320715,
JP08157361,	US5510368,	US5681842,	US5686460,	US5776967,
US5783597,	US5824699,	US5830911,	US5859036,	US5869524,
WO94/13635,	WO94/20480,	WO94/26731,	WO95/00501,	WO95/21817,
WO96/03385,	WO96/03387,	WO96/06840,	WO96/09293,	WO96/09304,
WO96/13483,	WO96/16934,	WO96/19462,	WO96/19463,	WO96/19469,
WO96/21667,	WO96/23786,	WO96/24584,	WO96/24585,	WO96/25405,
WO96/26921,	WO96/31509,	WO96/36617,	WO96/36623,	WO96/37467,
WO96/37469,	WO96/38418,	WO96/38442,	WO96/40143,	WO97/03953,
WO97/09977,	WO97/13755,	WO97/13767,	WO97/14691,	WO97/16435,
WO97/25045,	WO97/25046,	WO97/25047,	WO97/25048,	WO97/27181,
WO97/28120,	WO97/28121,	WO97/30030,	WO97/34882,	WO97/36863,

WO97/37984, WO97/38986, WO97/40012, WO97/46524, WO97/46532, WO98/03484, WO98/04527, WO98/06708, WO98/06715, WO98/07425, WO98/11080, WO98/15528, WO98/21195, WO98/22442, WO98/28292, WO98/29382, WO98/41511, WO98/41516, WO98/43966, WO98/45294, WO98/46594, WO98/46611, WO98/47890, WO98/51667, WO98/57924, WO99/01455, WO99/05104, WO99/10331, WO99/10332, WO99/11605, WO99/12930, WO99/14194, WO99/14195, WO99/14205, WO99/15505, ZA9704806 and ZA9802828;

as well as those mentioned in the following patent applications:

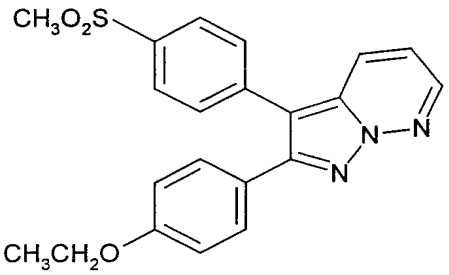
EP-921119, EP-937722, EP-985666, EP-1065204 DE19845446 US5916891, US6083969, JP11302266, JP2000136182, WO99/18093, WO99/23087, WO99/24404, WO99/25695, WO99/32448, WO99/33796, WO99/35130, WO99/37600, WO99/41224, WO99/43664, WO99/51559, WO99/58523, WO99/61436, WO99/62884, WO99/63939, WO99/64415, WO00/06576, WO00/08024, WO00/10563, WO00/10993, WO00/14082, WO00/17175, WO00/18753, WO00/20371, WO00/20398, WO00/23426, WO00/23433, WO00/26216, WO00/31063, WO00/32567, WO00/39116, WO00/40087, WO00/40243, WO00/50425, WO00/52008, WO00/55139, WO00/61571, WO00/66562 and PCT.EP00.11673 (unpublished at the filing date of the instant application);

all incorporated herein by reference (and hereinafter collectively referred to as the compounds of Group A). The above applications also describe, in relation to the COX-2 inhibitors they disclose, both suitable methods for their preparation and formulation, and doses for their administration.

In another aspect, the invention provides a method of treatment of a mammal, including man, suffering from a disorder ameliorated by a gastroprokinetic which comprises administering an effective amount of a compound of Group A or a pharmaceutically acceptable derivative thereof.

In another aspect, the invention provides the use of a compound of Group A or a pharmaceutically acceptable derivative thereof in the manufacture of a medicament for the treatment of a disorder ameliorated by a gastroprokinetic.

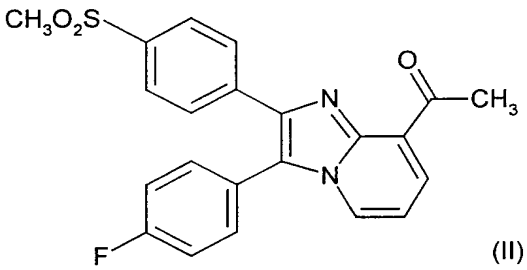
In the abovementioned WO99/12930 there is disclosed 2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine, which may be represented by formula (I)



(I)

and pharmaceutically acceptable derivatives thereof.

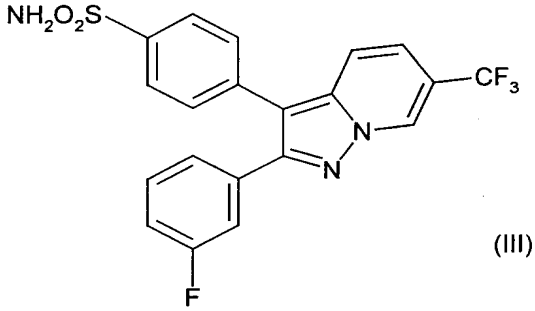
In the abovementioned WO96/31509 there is disclosed 8-acetyl-3-(4-fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-imidazo[1,2-a]pyridine, which may be represented by formula (II)



(II)

and pharmaceutically acceptable derivatives thereof.

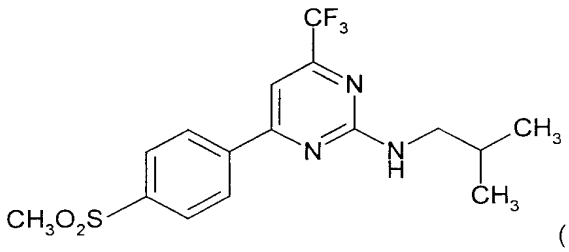
In the abovementioned WO00/26216 there is disclosed 4-[2-(3-fluoro-phenyl)-6-trifluoromethyl-pyrazolo[1,5-a]pyridin-3-yl]-benzenesulfonamide, which may be represented by formula (III)



(III)

and pharmaceutically acceptable derivatives thereof.

In the abovementioned PCT.EP00.11673 there is disclosed N-isobutyl-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidin-2-amine, which may be represented by formula (IV)



(IV)

and pharmaceutically acceptable derivatives thereof.

Further examples of compounds from within Group A include celecoxib, rofecoxib, valdecoxib and parecoxib; and pharmaceutically acceptable derivatives thereof.

Still further examples of compounds from within Group A include: etoricoxib (MK663); 4-(4-cyclohexyl-2-methyl-5-oxazolyl)-2-fluorobenzenesulfonamide (JTE-522); nimesulide; flosulide; 5,5-dimethyl-4-(4-methylsulfonylphenyl)-3-(2-propoxy)-5H-furanone, DFP; methanesulfonamide, N-(2-(cyclohexyloxy)-4-nitrophenyl) (NS398); and 5-methanesulfonamido-6-(2,4-difluorothiophenyl)-1-indanone (L-745337); and pharmaceutically acceptable derivatives thereof.

A further example of a compound from within Group A is COX 189.

It will be appreciated by the skilled person that, as a consequence of the use of different chemical naming conventions (e.g. IUPAC, CA and so on), the same compound may be referred to by different chemical names.

In another aspect, the invention provides a method of treatment of a mammal, including man, suffering from a disorder ameliorated by a gastroprokinetic which comprises administering an effective amount of:
2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine;
8-acetyl-3-(4-fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-imidazo[1,2-a]pyridine; 4-[2-(3-fluoro-phenyl)-6-trifluoromethyl-pyrazolo[1,5-a]pyridin-3-yl]-

benzenesulfonamide; N-isobutyl-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidin-2-amine; celecoxib; rofecoxib; valdecoxib; parecoxib; COX 189; etoricoxib (MK663); 4-(4-cyclohexyl-2-methyl-5-oxazolyl)-2-fluorobenzenesulfonamide (JTE-522); nimesulide; flosulide; 5,5-dimethyl-4-(4-methylsulfonylphenyl)-3-(2-propoxy)-5H-furanone (DFP); methanesulfonamide, N-(2-(cyclohexyloxy)-4-nitrophenyl) (NS398); or 5-methanesulfonamido-6-(2,4-difluorothiophenyl)-1-indanone (L-745337) (and hereinafter collectively referred to as the compounds of Group B);
or a pharmaceutically acceptable derivative thereof.

In another aspect, the invention provides the use of a compound of Group B or a pharmaceutically acceptable derivative thereof in the manufacture of a medicament for the treatment of a disorder ameliorated by a gastroprokinetic.

In another aspect, the invention provides a method of treatment of a mammal, including man, suffering from a disorder ameliorated by a gastroprokinetic which comprises administering an effective amount of 2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine or a pharmaceutically acceptable derivative thereof.

In another aspect, the invention provides the use of 2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine or a pharmaceutically acceptable derivative thereof in the manufacture of a medicament for the treatment of a disorder ameliorated by a gastroprokinetic.

Suitable pharmaceutically acceptable salts of 2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine include acid addition salts formed with inorganic or organic acids (for example hydrochlorides, hydrobromides, sulphates, phosphates, benzoates, naphthoates, hydroxynaphthoates, p-toluenesulphonates, methanesulphonates, sulphamates, ascorbates, tartrates, salicylates, succinates, lactates, glutarates, glutaconates, acetates, tricarballylates, citrates, fumarates and maleates), and solvates (for example hydrates) thereof.

Preferably, 2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine is employed in the form of its free base.

The invention includes all isomers of 2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine and its pharmaceutically acceptable derivatives, including all tautomeric and optical forms, and mixtures thereof, including racemic mixtures.

In another aspect the invention provides a COX-2 inhibitor or a pharmaceutically acceptable derivative thereof for use in the treatment of a disorder ameliorated by a gastroprokinetic.

In another aspect the invention provides a compound of Group A or a pharmaceutically acceptable derivative thereof for use in the treatment of a disorder ameliorated by a gastroprokinetic.

In another aspect the invention provides a compound of Group B or a pharmaceutically acceptable derivative thereof for use in the treatment of a disorder ameliorated by a gastroprokinetic.

In another aspect the invention provides celecoxib, rofecoxib, valdecoxib or parecoxib; or a pharmaceutically acceptable derivative thereof, for use in the treatment of a disorder ameliorated by a gastroprokinetic.

In another aspect the invention provides 2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine or a pharmaceutically acceptable derivative thereof for use in the treatment of a disorder ameliorated by a gastroprokinetic.

In another aspect the invention provides a COX-2 inhibitor or a pharmaceutically acceptable derivative thereof for use in the treatment of GORD.

In another aspect the invention provides a COX-2 inhibitor or a pharmaceutically acceptable derivative thereof for use in the treatment of ileus.

In another aspect the invention provides a COX-2 inhibitor or a pharmaceutically acceptable derivative thereof for use in the treatment of gastroparesis, such as diabetic gastroparesis.

In another aspect the invention provides a COX-2 inhibitor or a pharmaceutically acceptable derivative thereof for use in the treatment of NUD.

In another aspect the invention provides a COX-2 inhibitor or a pharmaceutically acceptable derivative thereof for use in the treatment of NCCP.

Within the above aspects of the invention, the use of a COX-2 inhibitor of Group A; such as a COX-2 inhibitor of Group B; for example celecoxib, rofecoxib, valdecoxib or parecoxib; in particular 2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine; is preferred.

It is to be understood that reference to treatment includes both treatment of established symptoms and prophylactic treatment, unless explicitly stated otherwise.

It will be appreciated by the skilled person that it may be advantageous to administer one (or more) other therapeutic agent(s) in combination with a COX-2 inhibitor for the treatment of gastroprokinetic ameliorated conditions. Examples of suitable therapeutic agents for adjunctive therapy include gastroprokinetic agents, such as cinitapride, cisapride, mosapride, itopride, prucalopride, idremcinal, lirexapride or metocloperamide; proton pump inhibitors, such as omeprazole, pantoprazole, rabeprazole, polaprezinc, lansoprazole, leminoprazole, esomeprazole and tenatoprazole; reversible proton pump antagonists, such as AR-H047108 and YH-1885; 5-HT_3 antagonists, such as alosetron; 5-HT_4 agonists, such as tegaserod; 5-HT_4 antagonists, such as piboserod; and H_2 antagonists, such as cimetidine, ebrotidine, famotidine, ranitidine, roxatidine, nizatidine, lafutidine, pibutine and osutidine; or pharmaceutically acceptable derivatives thereof.

In view of their surprising gastroprokinetic activity, COX-2 inhibitors may also be administered with one (or more) other therapeutic agent(s) to enhance the amount and rate of absorption of the other therapeutic agent(s). Examples of suitable therapeutic agents for such adjunctive therapy include 5-HT_1 receptor agonists, such as triptans (e.g. sumatriptan and naratriptan).

Thus in another aspect the invention provides the use, as a gastroprokinetic, of a COX-2 inhibitor, or a pharmaceutically acceptable derivative thereof, to enhance the amount of absorption of an orally administered $5HT_1$ receptor agonist, or a pharmaceutically acceptable derivative thereof.

In another aspect the invention provides the use as a gastroprokinetic of a COX-2 inhibitor, or a pharmaceutically acceptable derivative thereof, to enhance the rate of absorption of an orally administered $5HT_1$ receptor agonist, or a pharmaceutically acceptable derivative thereof.

It will be appreciated that adjunctive therapy may take the form of simultaneous or sequential coadministration of therapeutic agents and, when administration is sequential, either the COX-2 inhibitor or the other therapeutic agent (or one of the other therapeutic agents) may be administered first.

Conveniently, a COX-2 inhibitor or a pharmaceutically acceptable derivative thereof may be formulated in conventional manner using one or more pharmaceutically acceptable carriers or excipients. Thus a COX-2 inhibitor or a pharmaceutically acceptable derivative thereof may, for example, be formulated for oral, sub-lingual, buccal, parenteral, rectal or intranasal administration, or in a form suitable for administration by inhalation or insufflation (either through the mouth or nose), or in a form suitable for topical administration.

For oral administration the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrates (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters or ethyl alcohol); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid).

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

A COX-2 inhibitor or a pharmaceutically acceptable derivative thereof may be formulated for parenteral administration by injection, conveniently intravenous, intramuscular or subcutaneous injection, for example by bolus injection or continuous intravenous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, optionally with an added preservative.

The compositions for parenteral administration may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the compositions may be in dry form such as a powder, crystalline or freeze-dried solid for constitution with a suitable vehicle, e.g. sterile pyrogen-free water or isotonic saline before use. They may be presented, for example, in sterile ampoules or vials.

A COX-2 inhibitor or a pharmaceutically acceptable derivative thereof may also be formulated in rectal compositions such as suppositories or retention enemas.

Tablets for sub-lingual administration may be formulated in a conventional manner.

For intranasal administration, or administration by inhalation or insufflation, a COX-2 inhibitor or a pharmaceutically acceptable derivative thereof may be formulated in a conventional manner.

For topical administration the pharmaceutical compositions may be liquids, for example solutions, suspensions or emulsions presented in the form of creams or gels.

In addition to the formulations described previously, a COX-2 inhibitor or a pharmaceutically acceptable derivative thereof may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously, transcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compositions may be

formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

It will be appreciated that the precise therapeutic dose of a COX-2 inhibitor, expressed in the form of its free base, will depend on the age and condition of the patient and the nature of the disorder to be treated and will be at the ultimate discretion of the attendant physician.

However, in general, effective doses for the treatment of a disorder in man will lie in the range of 0.001 to 1000mg, such as 0.01 to 500mg, preferably 0.05 to 250mg, for example 0.5 to 100mg per unit dose, which could be administered in single or divided doses, for example, 1 to 4 times per day.

In a preferred embodiment, effective doses of 2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine for the treatment of a disorder in man will lie in the range of 0.1 to 1000mg, such as 1 to 500mg, preferably 10 to 250mg, for example 25, 50 or 100mg of 2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine per unit dose, which could be administered in single or divided doses, for example, 1 to 4 times per day.

The data that follows illustrates and supports the invention, but does not limit the invention in any way. Indomethacin is a non-selective COX inhibitor. Celecoxib, 8-acetyl-3-(4-fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-imidazo[1,2-a]pyridine and 2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine are selective COX-2 inhibitors. Cisapride is a gastroprokinetic agent.

Smooth Muscle *in vitro* model of gastric propulsion

Agents which stimulate antral smooth muscle activity would be expected to enhance the rate of gastric emptying by propulsion of contents in the aboral direction. By contrast, fundic relaxation could lead to delayed emptying of the stomach as the upper stomach would serve as a reservoir for gastric contents.

The effects of test agents were evaluated on strips of canine antrum circular muscles (n=4-8 strips) suspended in organ baths bathed with Krebs solution. Following establishment of baseline tension, acetylcholine ("ACh"; 1μM),

indomethacin (10μM), or 8-acetyl-3-(4-fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-imidazo[1,2-a]pyridine ("8-Acetyl- ... "; 10μM) were applied and tension changes monitored and recorded on a polygraph.

The nonselective COX inhibitor, indomethacin, was observed to sensitise antral circular muscle segments to the addition of acetylcholine, such that enhanced acetylcholine-induced contractions were noted following treatment with indomethacin. The effects of the selective COX-2 inhibitor 8-acetyl-3-(4-fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-imidazo[1,2-a]pyridine were also evaluated on antral mechanical activity and produced a similar degree of sensitisation for acetylcholine-induced contractility as seen with indomethacin (fig 1).

By contrast to the above results, strips of canine fundic circular muscle (n=6-8) showed a complete relaxation following treatment with sodium nitroprusside (SNP, 10μM) and a near complete relaxation following indomethacin (10μM). 8-Acetyl-3-(4-fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-imidazo[1,2-a]pyridine (10μM), on the other hand, produced only small changes in tension (fig 2).

The motility consequences of such differences appear to represent the explanation for the enhancement of gastric emptying by selective COX-2 inhibitors, but not indomethacin. Differences seen with indomethacin and 8-acetyl-3-(4-fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-imidazo[1,2-a]pyridine appear to represent a consequence of inhibition of synthesis of COX-1 mediated products by indomethacin which would not be seen with the selective COX-2 inhibitor.

Changes in mechanical activity following administration of 8-acetyl-3-(4-fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-imidazo[1,2-a]pyridine are suggestive of constitutive expression of COX-2. Constitutive production of COX-2 mRNA in dog antral, duodenal and colonic smooth muscle was confirmed by polymerase chain reaction (PCR) and provides strong support for the utility of COX-2 inhibitors as gastroprokinetics (fig 5).

Activity in vivo: Dog model of gastric emptying

Beagle dogs were treated for three days with test agents (po administration): placebo BID; cisapride 0.14 mg/kg TID; celecoxib 2.8 mg/kg BID; or 8-acetyl-3-(4-fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-imidazo[1,2-a]pyridine 1.2 mg/kg BID. Solid phase gastric emptying was measured on the fourth day following am dosing. The same three animals were used for evaluation of each agent, thus reducing any interanimal variations.

Isotope-labeled solid food was fed to the dogs for their morning meal and animals were then placed under a gamma camera and scans performed over the 24 to 36 hours.

Cisapride, celecoxib and 8-acetyl-3-(4-fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-imidazo[1,2-a]pyridine all increased the rate of gastric emptying (fig 3). Thus, treatment with COX-2 inhibitors enhances the rate of gastric emptying and hence COX-2 inhibitors serve as gastroprokinetic agents.

Activity *in vivo*: Dog model of lower esophageal sphincter pressure (LESP)

Six adult dogs were instrumented with 14 French esophagostomy tubes. Animals were treated for 3 days with placebo (BID), cisapride (0.14 mg/kg TID) or celecoxib (1.2 mg/kg BID). On day 4 dogs received their am dose of test agent and water perfused manometry catheters were inserted through the esophagostomy tubes. Lower esophageal sphincter pressures (LESPs) were then monitored.

Cisapride increased LESP as compared to placebo treated animals. Celecoxib was noted to increase LESP to a similar degree as cisapride (fig 4).

Thus, in addition to speeding gastric emptying, COX-2 inhibitors display a second characteristic of gastroprokinetic agents, that of increasing LESP. Increasing LESP would be of therapeutic benefit in preventing reflux of materials from the stomach to the esophagus.

Activity *in vivo*: Rat model of post operative ileus

The selective COX-2 inhibitor 2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine was evaluated in a rat model of post-operative ileus. The methodology represents a modification of the procedure described by McGill *et al,* Gastroenterology 116: A1040 (1999).

Rats (fourteen) received 0.5 cc of skimmed milk with methylene blue by gavage. Either vehicle (six rats) or 2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine (eight rats) was then administered by intravenous infusion. Rats were sacrificed four hours post-gavage and the distance the methylene blue meal traversed the intestine measured. The pylorus was set at 0 cm. With vehicle treatment, the meal traversed 49.3 $\pm$ 1.3 cm while with 2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine (3 mg/kg), the meal traversed 67.8 $\pm$ 1.1 cm ($p<0.05$).

Thus the selective COX-2 inhibitor 2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine produced a significant stimulation in gastrointestinal transit.

Claims

1. A method of treatment of a mammal, including man, suffering from a disorder ameliorated by a gastroprokinetic which comprises administering an effective amount of a COX-2 inhibitor or a pharmaceutically acceptable derivative thereof.

2. A method of treatment according to claim 1 wherein the disorder is GORD.

3. A method of treatment according to claim 1 wherein the disorder is ileus.

4. A method of treatment according to claim 1 wherein the disorder is gastroparesis.

5. A method of treatment according to claim 1 wherein the disorder is NUD.

6. A method of treatment according to claim 1 wherein the disorder is NCCP.

7. A method of treatment according to any one of claims 1 to 6 wherein the COX-2 inhibitor is 2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine; 8-acetyl-3-(4-fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-imidazo[1,2-a]pyridine; 4-[2-(3-fluoro-phenyl)-6-trifluoromethyl-pyrazolo[1,5-a]pyridin-3-yl]-benzenesulfonamide; N-isobutyl-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidin-2-amine; celecoxib; rofecoxib; valdecoxib; parecoxib; COX 189; etoricoxib (MK663); 4-(4-cyclohexyl-2-methyl-5-oxazolyl)-2-fluorobenzenesulfonamide (JTE-522); nimesulide; flosulide; 5,5-dimethyl-4-(4-methylsulfonylphenyl)-3-(2-propoxy)-5H-furanone (DFP); methanesulfonamide, N-(2-(cyclohexyloxy)-4-nitrophenyl) (NS398); or 5-methanesulfonamido-6-(2,4-difluorothiophenyl)-1-indanone (L-745337);
or a pharmaceutically acceptable derivative thereof.

8. A method of treatment according to any one of claims 1 to 7 wherein the COX-2 inhibitor is 2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine or a pharmaceutically acceptable derivative.

9. A method of treatment according to claim 8 wherein 2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine is in the form of its free base.

10. Use of a COX-2 inhibitor or a pharmaceutically acceptable derivative thereof in the manufacture of a medicament for the treatment of a disorder ameliorated by a gastroprokinetic.

11. Use according to claim 10 wherein the disorder is GORD.

12. Use according to claim 10 wherein the disorder is ileus.

13. Use according to claim 10 wherein the disorder is gastroparesis.

14. Use according to claim 10 wherein the disorder is NUD.

15. Use according to claim 10 wherein the disorder is NCCP.

16. Use according to any one of claims 10 to 15 wherein the COX-2 inhibitor is 2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine; 8-acetyl-3-(4-fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-imidazo[1,2-a]pyridine; 4-[2-(3-fluoro-phenyl)-6-trifluoromethyl-pyrazolo[1,5-a]pyridin-3-yl]-benzenesulfonamide; N-isobutyl-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidin-2-amine; celecoxib; rofecoxib; valdecoxib; parecoxib; COX 189; etoricoxib (MK663); 4-(4-cyclohexyl-2-methyl-5-oxazolyl)-2-fluorobenzenesulfonamide (JTE-522); nimesulide; flosulide; 5,5-dimethyl-4-(4-methylsulfonylphenyl)-3-(2-propoxy)-5H-furanone (DFP); methanesulfonamide, N-(2-(cyclohexyloxy)-4-nitrophenyl) (NS398); or 5-methanesulfonamido-6-(2,4-difluorothiophenyl)-1-indanone (L-745337);
or a pharmaceutically acceptable derivative thereof.

17. Use according to any one of claims 10 to 16 wherein the COX-2 inhibitor is 2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine or a pharmaceutically acceptable derivative.

18. Use according to claim 17 wherein 2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine is in the form of its free base.

19. A COX-2 inhibitor or a pharmaceutically acceptable derivative thereof for use in the treatment of a disorder ameliorated by a gastroprokinetic.

20. The use, as a gastroprokinetic, of a COX-2 inhibitor, or a pharmaceutically acceptable derivative thereof, to enhance the amount of absorption of an orally administered $5HT_1$-like receptor agonist, or a pharmaceutically acceptable derivative thereof.

21. The use, as a gastroprokinetic, of a COX-2 inhibitor, or a pharmaceutically acceptable derivative thereof, to enhance the rate of absorption of an orally administered $5HT_1$-like receptor agonist, or a pharmaceutically acceptable derivative thereof.

Fig 1

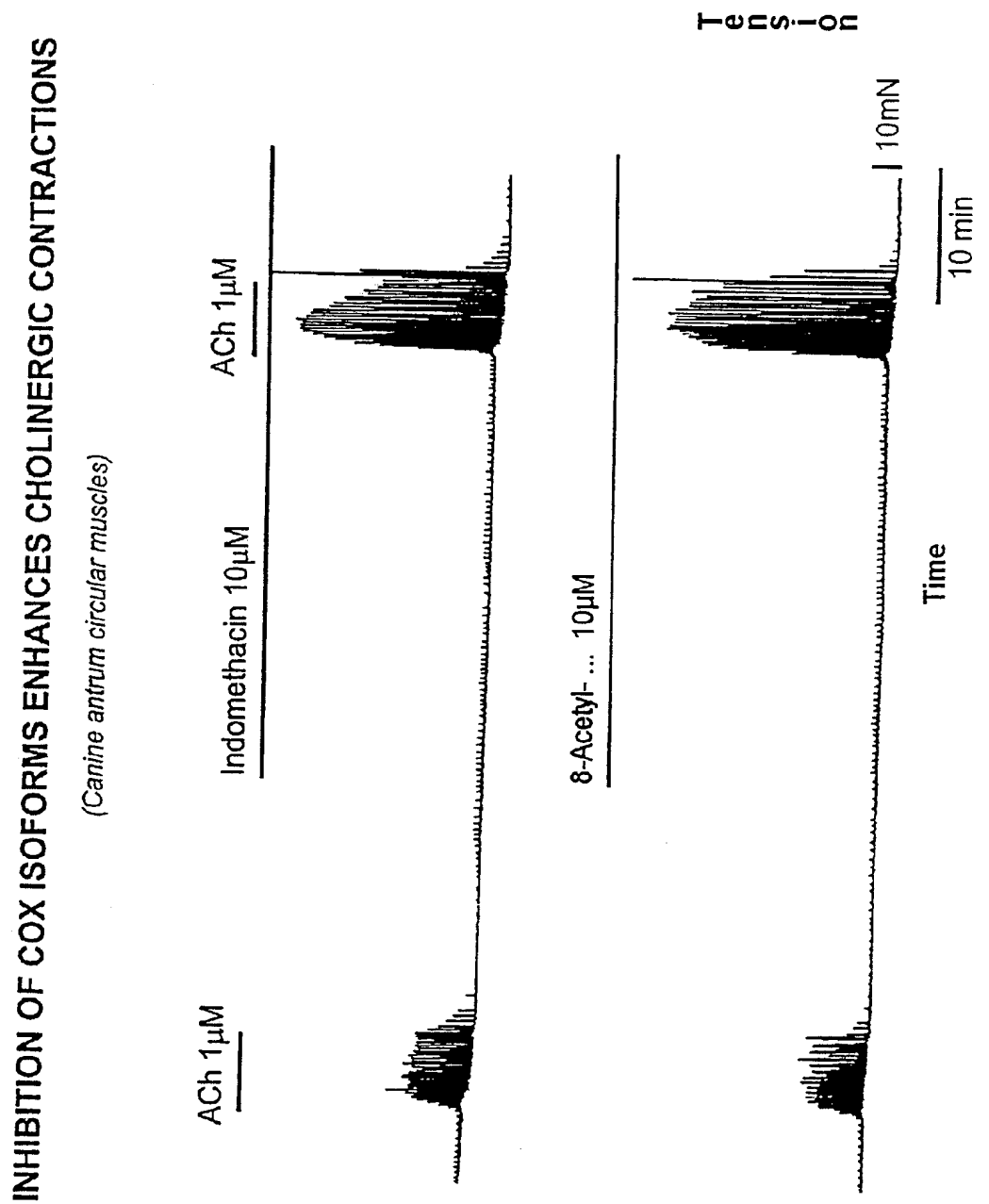

INHIBITION OF COX ISOFORMS ENHANCES CHOLINERGIC CONTRACTIONS
(Canine antrum circular muscles)
ACh 1μM
Indomethacin 10μM
ACh 1μM
8-Acetyl-... 10μM
Tension
10mN
10 min
Time

Fig 2

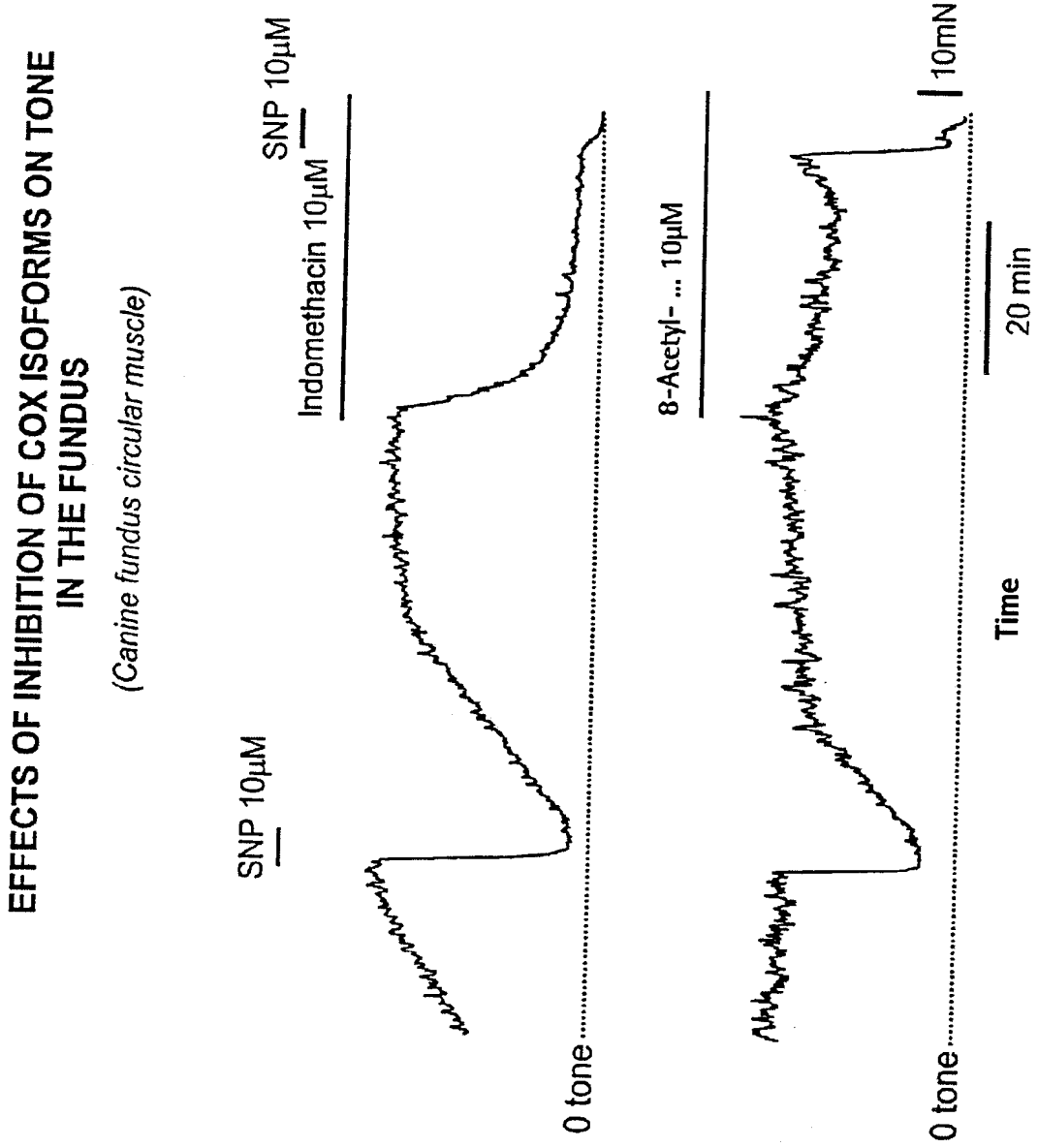

EFFECTS OF INHIBITION OF COX ISOFORMS ON TONE IN THE FUNDUS
(Canine fundus circular muscle)
SNP 10μM
SNP 10μM
Indomethacin 10μM
0 tone
8-Acetyl- ... 10μM
Tension
10mN
20 min
Time
0 tone

Fig 3

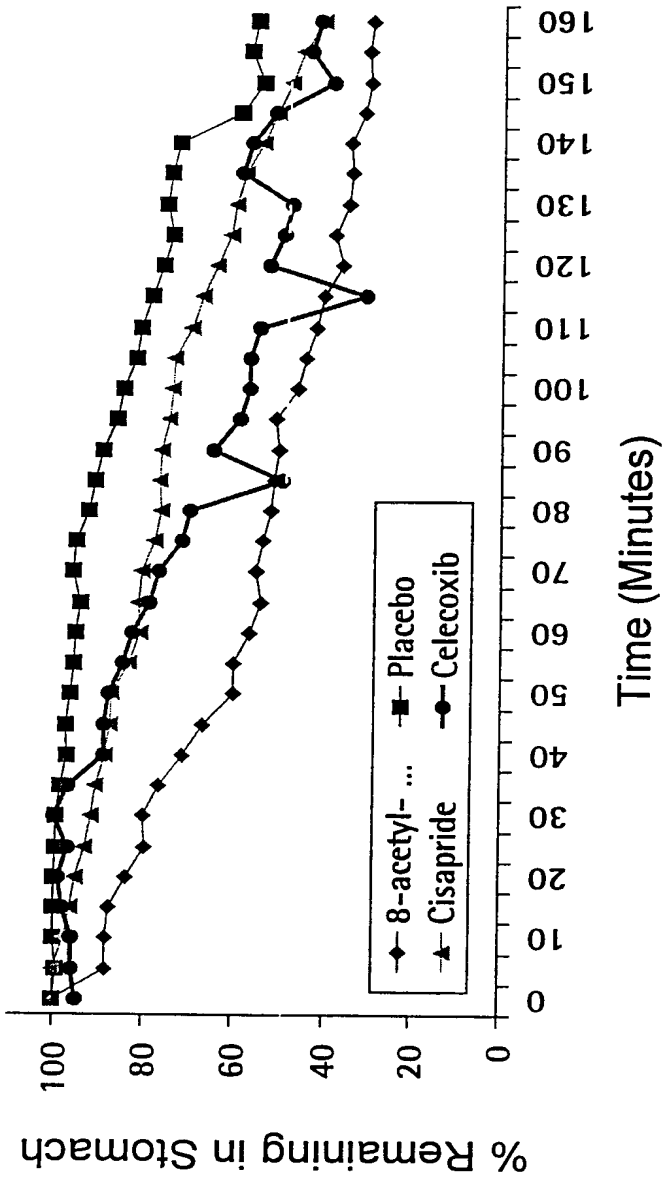

% Remaining in Stomach
100
80
60
40
20
0
Time (Minutes)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
8-acetyl- ...
Placebo
Cisapride
Celecoxib

Fig 4

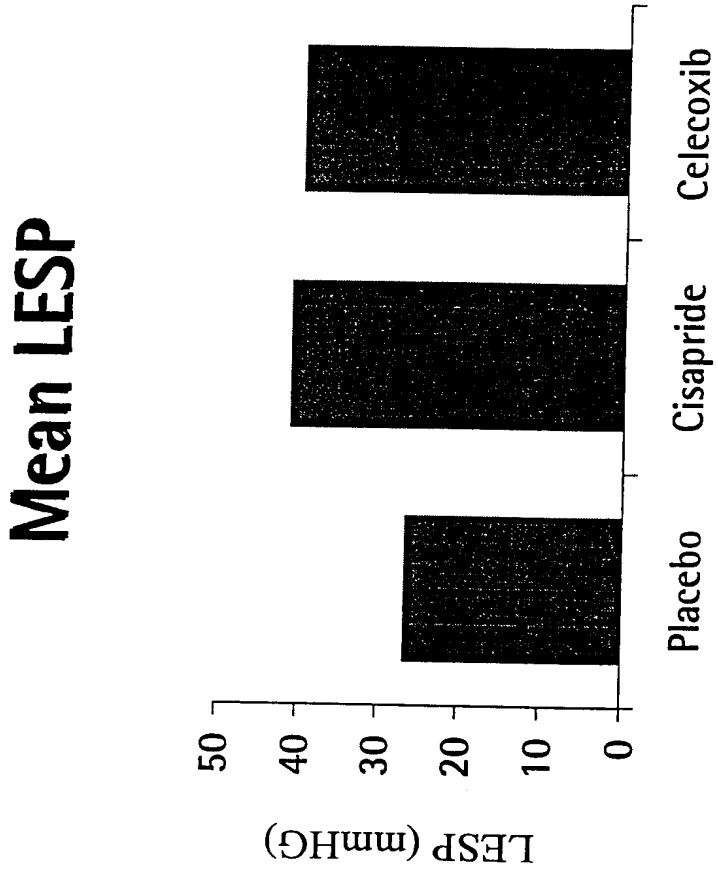
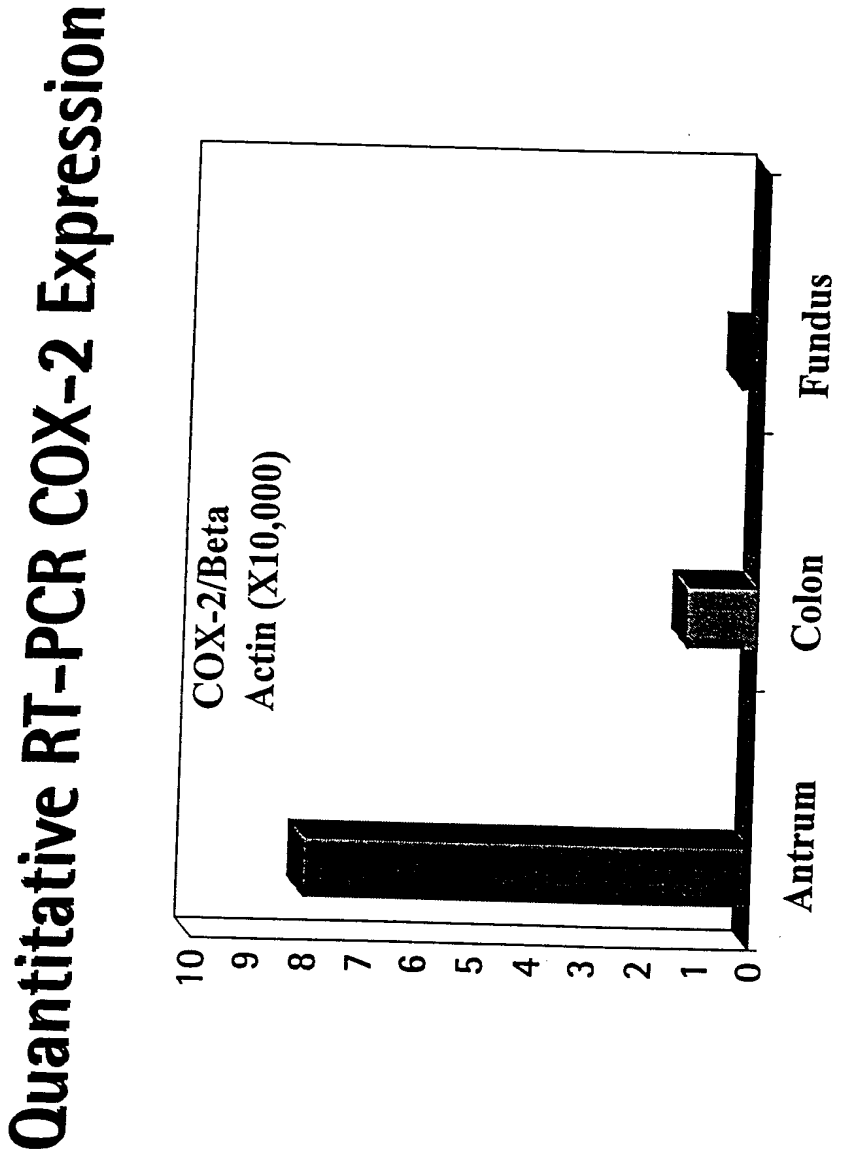

Mean LESP
LESP (mmHG)
50
40
30
20
10
0
Placebo
Cisapride
Celecoxib

Fig 5


Quantitative RT-PCR COX-2 Expression
COX-2/Beta
Actin (X10,000)
10
9
8
7
6
5
4
3
2
1
0
Antrum
Colon
Fundus

INTERNATIONAL SEARCH REPORT

.national Application No
PCT/GB 01/00423

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/445 A61K31/415 A61P1/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, EMBASE, CHEM ABS Data, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HAYAKAWA T. ET AL: "Effects of Dai-Kenchu-To on Intestinal Obstruction following Laparatomy" J. SMOOTH MUSCLE RES., vol. 35, no. 2, 1999, pages 47-54, XP000995643 abstract	1,3,10, 12,19
Y	page 53	1-19
X	JOSEPHS M.D. ET AL: "Products of Cyclooxygenase-2 Catalysis regulate Postoperative Bowel Motility" JOURNAL OF SURGICAL RESEARCH, vol. 86, no. 1, 1999, XP000996009 page 52, right-hand column	1,3,7, 10,12, 16,19
Y	page 53	1-19

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 April 2001	15.06.01

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Brunnauer, H

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 01/00423

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	MORGAN G.: "Beneficial Effects of NSAIDs in the Gastrointestinal Tract." EUROPEAN JOURNAL OF GASTROENTEROLOGY AND HEPATOLOGY, vol. 11, no. 4, 1999, pages 393-400, XP000996052 page 395, right-hand column	1,2,10, 11,19
Y	page 399	1-19
X	EP 0 812 591 A (PANACEA BIOTEC LTD) 17 December 1997 (1997-12-17) claim 1	19
A	GB 2 325 161 A (MERCK SHARP & DOHME) 18 November 1998 (1998-11-18) page 3, line 5 - line 26	20,21
P,X	WO 00 48583 A (POZEN INC) 24 August 2000 (2000-08-24) page 1, line 1 - line 15 page 5, line 8 - line 25	20,21

INTERNATIONAL SEARCH REPORT

international application No.
PCT/GB 01/00423

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: -
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-6 and 10-15 relate to an extremely large number of possible compounds/methods, since agents are defined by functional terms (COX-2 inhibitors). Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds/methods claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds/methods of claims 7-9 and 16-18.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 01/00423

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0812591 A	17-12-1997	AU 693720 B	02-07-1998
		CA 2188703 A	24-04-1998
		CZ 9603166 A	13-05-1998
		JP 2875988 B	31-03-1999
		JP 10130143 A	19-05-1998
		NO 964189 A	06-04-1998
		NZ 299481 A	22-09-1997
		AU 6799396 A	09-04-1998
		HU 9601442 A	28-04-1998
		US 5716609 A	10-02-1998
		US 5688829 A	18-11-1997
GB 2325161 A	18-11-1998	NONE	
WO 0048583 A	24-08-2000	AU 3596500 A	04-09-2000